June 23, 2004

On May 19 and 20, the NIH Office of AIDS Research sponsored an Ad Hoc Working Group on the NIAID plan for restructuring the AIDS clinical trials networks for therapeutics, vaccines, and prevention initiatives. The charge to the Ad Hoc Working group was to develop a series of principles that will guide the formulation of the funding initiatives for restructuring the networks. The Working Group is providing the common themes of the principles so that ARAC can take these into consideration as that Advisory Group undertakes the review of the three concepts for restructuring the NIAID clinical trials networks. This statement represents broad principles the Working Group feels are important to ensure that effective and efficient clinical trials networks result from the restructuring process. This statement should not be interpreted to mean that the current three concepts developed by DAIDS have omitted or not taken into consideration any or all of these principles.

1. Over the past few years, clinical trials networks have sometimes not undertaken high priority research protocols that could not be implemented by the network site infrastructure; some networks have unnecessarily focused on multi-site, even multinational protocols – because the network consisted of a large number of funded sites existing in many countries. Clinical trial networks have not moved quickly to design and support operational research, even though such research has been prioritized by NIH, and by a forthcoming IOM report on scaling up ART in developing countries. This may be because the network infrastructure (both physical and human resources) – lacks expertise in operational research. The international sites for some networks have been developed through domestic sites not necessarily experienced in international HIV/AIDS research.

   Principle 1: The highest priority science must drive the structure of NIAID's clinical trials endeavor, rather than vice-versa. The structure/mechanism of how NIAID's resources are used for clinical research must be flexible and serve the scientific priorities. The Working Group feels that one mechanism will be unable to accomplish the breadth of the clinical research that needs to be conducted. For example, laboratory-based clinical translational research of short or moderate duration may be optimally conducted in the context of a standing network funded to conduct multiple similar research projects. However, operational research projects that require very large numbers of patients and/or long-term follow-up (i.e., operational/treatment strategy research or vaccine effectiveness studies) may be optimally conducted as a single study investigator-initiated project or as a coordinating center grant. Alternatively, operational research on scaling-up ART as part of primary health care delivery in resource poor settings (Africa, Asia, South America, the Caribbean, etc.) may require development of dispersed rural research sites as a network coordinated by an urban center, rather than the urban site *per se*. The integration of HIV prevention (biologic as well as socio-behavioral) and treatment is a key public health and

scientific priority. Thus, structural linkages between programs of research on prevention interventions and optimizing HIV treatments with programs for delivery of prevention interventions and treatment may be necessary. Scientific leadership, decision-making, and initiation of research ideas are best placed in the hands of those actually conducting the clinical research and, as such, clinical research structures should be established to support this principle. As scientific priorities may shift, research support mechanisms must be flexible enough to incorporate new ideas and new investigators to address the science. DAIDS must support a variety of types of clinical research structures in order to address the highest priority science.

2. Over the past year, the definition of clinical trials research priorities by DAIDS has been evolving from very general to more specific descriptions of priorities, but international and domestic site representatives are requesting still more specific discussion of DAIDS' priorities. The individual networks have begun to present more explicit descriptions of research priorities, but these are now sometimes expressed in all-encompassing lists, not limited to clinical trials *per se*. Scientific priorities that require clinical trials that cannot be conducted within the resources of these networks are not articulated.

   Principle 2: DAIDS scientific priorities for AIDS clinical research in the areas of therapeutics, vaccines, and prevention should be more clearly defined now, be integrated with and reflect the priorities and plans of other NIH HIV/AIDS research endeavors, and be reassessed annually. The annual NIH plan for HIV-Related Research should be used as a guide to develop these specific priority questions along with regular communication between NIAID and the other NIH Institutes, Centers and Divisions that support HIV/AIDS clinical research. The ARAC should assist DAIDS in elaborating and prioritizing these questions and ARAC is encouraged to convene specific meetings with expert ad hoc members (national or international), as needed. These scientific priorities should then inform the structure of DAIDS' clinical trials endeavors.

3. Objectivity and transparency are critical in evaluation and selection of major proposed clinical trials protocols that will use DAIDS (network or non-network) resources. Selection should be based on explicit criteria that include the NIH, DAIDS, and ARAC prioritization discussed above. Further, an independent external group has not regularly reviewed the DAIDS-funded clinical trials networks. Only the HPTN has been externally reviewed during the past 2 years, and several changes to it were recommended.

   Principle 3a: Objective external review of major clinical trials should be routine. The major clinical trials to be conducted by the networks should undergo objective external review – perhaps by standing advisory committees, such as the AIDS Vaccine Research Working Group or by ARAC, supplemented by appropriate ad hoc national or international experts.

Principle 3b: Regular external evaluation of the progress of the standing networks should be conducted and that oversight should be integrated into network operations. The ARAC is the logical group to conduct network evaluations. Supplementing ARAC with clinical trials experts, and experts in operations or effectiveness research would be appropriate as needed.

4. Community advisory boards are comprised of volunteers, and their needs, effectiveness, and impact, require evaluation, along with the other key components of networks

   Principle 4: Community involvement and participation must be routinely incorporated into all components of DAIDS-supported clinical research and supported through specific mechanisms with investment of resources (for education, technical assistance, and to ensure meaningful involvement, etc.). An evaluation of the effectiveness of community involvement should also be integrated into all DAIDS-supported clinical research activities.

5. The timeline for development and implementation of clinical trials protocols in some DAIDS-supported networks has been too lengthy and DAIDS must focus its creative energies and experience on improvement in the area.

   Principle 5: Protocol development and implementation must be streamlined and be appropriate for the science being conducted. Streamlined protocol development and implementation should minimize DAIDS staff (or contractor) involvement. Serious consideration should be given to establishment of interdisciplinary project management teams for each project that would be provided sufficient resources and fixed deadlines to develop and implement each stage of new product or intervention evaluation.

6. The proliferation of clinical trials in some international settings has led to many redundancies. For example, DAIDS supports several laboratories in Kampala alone. This plethora of overlapping and redundant resources needs better coordination.

   Principle 6: To provide better coordination and efficiency and avoid redundancy, strong incentives should be given for intra-country communications and collaboration between all similar resources (i.e., reference labs, research support contracts, community input, etc. supported by NIH [all Institutes, Centers and Divisions], but also by CDC, EU/EDCTP, ANRS, MRC, WHO, philanthropy, etc.). Promotion of local or in-country scientific and administrative leadership, ownership and investment in the research enterprise could also promote improved coordination and efficiency.

7. Redundancies can potentially exist not only at the international and domestic research sites, but also in the core research support services (statistical leadership,

data management, data analysis, administrative support, and operation centers) and even in the missions of the networks.

Principle 7a: Duplication of network core resources should be minimized wherever possible by use of common resources. For example, common data management, operations, and administrative support functions should be considered/used if DAIDS funds more than one clinical research network to conduct multiple trials. In order to retain the flexibility needed to best address scientific priorities (for example the conduct of trials with very large numbers of patients, i.e., sample size of thousands, and/or long-term follow-up, i.e., for 5, 10 years or more), will likely need independent research resources distinct from those of standing research networks.

Principle 7b: Avoidance of redundancy in network missions is desirable. Existing or potential overlap in network missions can lead to confusion, competition for precious resources, and inefficiency. For example, redundancy in network mission could allow international or domestic network sites to submit or participate in similar protocols through multiple networks sequentially or even simultaneously. Coordination and communication among trials leadership, including statistical leadership, will be required to minimize redundancy.

8. Research in resource poor settings is not conducted in a vacuum. The many ethical considerations and needs of future research and development have been discussed elsewhere. Thus, a commitment to catalyzing capacity building and local/regional development are key to incorporate into all DAIDS-sponsored clinical research programs.

   Principle 8: Training and capacity building that promotes local or in-country ownership/investment in the research enterprise must accompany research support for sites in both U.S. and international resource-poor settings. DAIDS supported clinical research in resource poor settings (domestic or international) must catalyze linkages that will foster training and capacity building perhaps in part through linkages to CIPRA, CFAR, AITRP, ICOHRTA, perhaps with network support for junior investigators trained by CIPRA, CFAR, and Fogarty International Center programs. In addition, non-NIH linkages should be sought with other sources for training and capacity building such as governmental agencies, foundations, and other health organizations. All research proposals conducted in resource poor settings must contain a clear and convincing training and capacity building component in order to be eligible for NIAID funds.

9. There exists the perception that some existing networks have spent so much of their funding on infrastructure that little or no funds were left to conduct clinical trials. Some sites have used infrastructure funding to conduct studies other than clinical trials while waiting for the trials to begin. For example, potentially better and more appropriate mechanisms exist for review and support of studies on the epidemiology and pathogenesis of HIV infection. The dilemma of funding

networks with no clinical trials to carry out versus important clinical trials with no network funding or ability to carry them out has been a chronic problem for over a decade for both past and present HIV clinical trials networks. At least one network, and likely many, has also found it very difficult to de-fund non-performing sites.

Principle 9: DAIDS clinical research funding should support appropriate levels of infrastructure and provide DAIDS-controlled incentives to support the direct costs for the conduct of clinical trials. Funding of fixed costs for central and clinical site infrastructure should be balanced with funding for incremental and variable costs required for the conduct of a specific clinical trial. In this way, clinical research funds are held in reserve to support the major trials approved by a review committee. The goals are to "incentivize" timely conduct of essential research and to retain sufficient funds in reserve to actually fund the research. For example, a portion of DAIDS' total $400M for clinical trials – perhaps a third – could be committed to sustaining and building infrastructure, while the remainder could be allocated across networks, to fund approved trials, as well as the additional infrastructure needed to conduct these trials.